REMARKS

The Office Action dated December 30, 2008 has been carefully reviewed and the foregoing amendment and the following remarks are made in response thereto. Applicants respectfully request reconsideration of this application and timely allowance of the pending claims.

Status of the Claims

New claim 89 has been added to further defines the characterized biosystem as animal cells or tissues. Support for this amendment can be found throughout the application as originally filed. Specific support can be found at least at page 44, line 20; page 47, line 21; and page 51, line 28 to page 52, line 1. Thus, the above amendment does not introduce any prohibitive new matter to the original disclosure.

Upon entry of the above amendment, claims 83, 84, and 87 to 89 are pending in the present application.

Claim Rejection under 35 U.S.C. § 103(a)

Claims 83, 84, 87, and 88 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Khwaja et al. (U.S. Patent No. 6,113,907) in view of Lockhart et al. (U.S. Patent No. 6,040,138) or Xiong et al. (Molecular Breeding, 1998, vol. 4, 129-136) and Wallace et al. (Molecular Medicine Today, 1997, vol. 3, 384-389), and further in view of Ray et al. (U.S. Patent No. 4,570,380). Specifically, the Examiner alleges that it would have been obvious to one skilled in the art at the time of the invention to replace the bioassay of Khwaja et al. with the assay as described by Lockhart et al., Xiong et al., or Wallace et al. to obtain a quality control method as the present application claims.

Applicants respectfully disagree with the Examiner's conclusion because the Examiner has used impermissible hindsight reconstruction based on Applicants' own disclosure to combine and modify the prior art to arrive at this clearly erroneous conclusion of obviousness and Applicants hereby traverse the rejections as follows.

First, there is no disclosure or suggestion provided in the cited references, or otherwise on the record, which would motivate one skilled in the art to combine and modify the methods of the cited references in such a particular way to obtain the claimed method which, among other things, tests herbal compositions as whole samples, not fractionations thereof, via a genomic-based assay using one biosystem.

Khwaja et al. disclose the use of compositional and activity fingerprints in the processing of St. John's Wort materials to produce pharmaceutical grade compositions (Abstract). Specifically, the Khwaja method involves the steps of obtaining a sample of a botanical material; conducting fractionation by separating/isolating the sample into multiple fractions; performing bioassay by measuring the biological activity of each individual fractions against a biomarker, such as an enzyme or receptor; and establishing the "fingerprint" according to the biological activity for each of the fractions (Figure 1; column 12, line 61 to column 13, line 21; and column 17, lines 6 to 23).

The claimed method is markedly different from the Khwaja method in at least two aspects. First, the claimed method does not involve fractionation of the sample, i.e., the herbal composition. In claimed method, the herbal composition is tested as a whole sample without fractionation. In contrast, the Khwaja sample, regardless of a whole plant or plant parts, is separated into multiple fractions before testing. Second, the claimed method tests the whole sample via a genomic-based assay to determine its differential gene expression profile, while the Khwaja method tests each individual fractions of the sample via bioassay to determine the biological activity of each individual fractions.

Inasmuch as the marked difference from the claimed method, Khwaja et al. do not suggest in any way that the fractionation step be eliminated or the bioassay be replaced by a genomic-based assay. In fact, Khwaja et al. repeatedly emphasize the necessity of fractionation of the sample as shown below:

> "The procedure involves separating the aliquot of botanical material into a plurality of marker fractions wherein each of the marker fractions includes at least one of the active components or in some cases one of the inactive components." (underline added, column 13, lines 12 to 14)
>
> "For establishing a pharmaceutical fingerprint (PharmaPrint®) in accordance with the present invention, the plant is extracted according to the

procedure as set forth in FIG. 3 to separate it into major components..." (underline added, column 17, lines 6 to 10)

"Once the sample extract has been prepared and/or alternatively purchased as a commercially available extract, a portion needs to be subjected to fractional analysis. If the fingerprint has already been established, the sample or aliquot is separated into the same plurality of marker fractions which are present in the standard fingerprint." (underline added, column 22, lines 15 to 20)

"For some materials only a few marker fractions are required. For other more complex materials, there may be numerous marker fractions." (underline, column 22, lines 24 to 26)

Thus, the specific teachings of fractionation in Khwaja et al. directly contradict the claimed method which tests the whole sample without fractionation.

Lockhart et al. describe methods of monitoring the expression levels of a multiplicity of genes and further suggest using the method to determine the expression levels of a disease marker for the purpose of diagnosing the disease (Abstract; and column 4, lines 64 to 67). In contrast, detection of disease is irrelevant to the genomic-based assay in the claimed method since the present genomic-based assay is not limited to determining the expression levels of any particular disease marker. More importantly, Lockhart et al. are completely silent as to using the method disclosed therein for controlling the quality of herbal compositions.

The Examiner has asserted that the Lockhart method can be used for identifying differential gene expression between two samples. In response, Applicants respectfully note that, in the context of differential gene expression, the two Lockhart samples are a pathological sample and a healthy sample as indicated by the paragraph cited by the Examiner:

"The expression monitoring methods of this invention may be used in a wide variety of circumstances including detection of disease, identification of differential gene expression between two samples (e.g., a pathological as compared to a healthy sample)..." (underline added, column 10, lines 22 to 26)

That is, the Lockhart method uses two different biosystems, i.e., a pathological biosystem and a healthy biosystem, to obtain differential gene expression. In contrast, the claimed method uses only one biosystem to obtain differential gene expression. Specifically, as recited by independent claim 83, a biosystem is exposed to a standardized batch of an herbal composition in step (b)(i) and the same biosystem is also exposed to a test batch in step (c)(i). More

importantly, the Lockhart method requires at least two different biosystems because the comparison is between a healthy biosystem and a second biosystem for the purpose of diagnosing diseases in the second biosystem, while the claimed method requires a single biosystem because the comparison is between two or more herbal compositions while the biosystem functions as a measuring device. More specifically, in order to assure the consistency in comparing different herbal compositions in the claimed method, the measuring device, i.e., the biosystem, has to be the same for each herbal compositions. Therefore, with respect to differential gene expression, Lockhart et al. teach away from the claimed invention.

Xiong et al. use differential display analysis to assess the patterns of differential gene expression in hybrids relative to their parents in certain rice plants. It is important to note that Xiong et al. focus on the genetics and gene expression profile of the rice plants themselves for plant identification. That is, the differential gene expression in Xiong et al. is that of botanical materials, i.e., rice plants. In contrast, the differential gene expression in the claimed method is that of a biosystem, not that of the botanical materials. Inasmuch as focusing on rice plants themselves, Xiong et al. do not disclose or remotely suggest exposing a biosystem to botanical samples and determining the differential gene expression of the biosystem as the claimed method recites.

Wallace discuss the use of genomic-based technology for diagnostics and research. However, Wallace is completely silent as to using genomic-based technology for controlling the quality of herbal compositions, let alone disclosing or suggesting the particulars of testing herbal compositions as whole samples via a genomic-based assay by using a single biosystem as the present application claims.

Ray et al. disclose a method for hybrid cotton production by utilizing a cytoplasmic-genetic male sterile system for forming F1 hybrid cottonseeds. However, Ray et al. do not even remotely mention genomic-based assay or differential gene expression. Although Ray et al. discuss gene pairs to some extent, such discussion is directed to the correlation between certain gene pairs and the plant leaf configuration and is not related to genomic-based assay or differential gene expression at all.

With respect to raising an obviousness rejection, the United States Supreme Court in *KSR Int'l Co. v. Teleflex* expressed the need to an "explicit" showing of "some apparent reason to

combine the known elements in the fashion claimed by the patent at issue" and that "rejection on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 127 S.Ct. 1727, slip op. at 14 (2007).

In view of the foregoing, not only the combined disclosures of the cited references fail to suggest combining and modifying the disclosed methods in the fashion claimed by the present application, but Khwaja et al. and Lockhart et al. contradict and teach away from the claimed method. As stated in the Declaration under 37 C.F.R. §1.132 by Dr. Dan Theodorescu dated March 7, 2005, Dr. Theodorescu (paragraph 6, pages 6 to 7), a person of ordinary skill in the art who was aware of gene expression technology and the need for botanical quality control, did not envision applying genomic-based assay to botanical quality control in such a particular way to arrive at the claimed method at the time of the present invention. Thus, Applicants believe the §103 rejection is based on impermissible hindsight reconstruction of the cited references which gleans knowledge from Applicants' own disclosure, and thereby should be withdrawn.

Furthermore, there are long felt but unresolved needs and failure of others for the development of a method of controlling the quality of herbal compositions. Specifically, despite the fact that herbal medicines have been used for many centuries in the treatment of various diseases, more advanced development of herbal medicines has been hindered by the unique problem of unpredictable variability of herbal medicines due to the lack of quality control method (page 1, line 10 to page 2, line 7, and page 7, line 22 to page 8, line 6 of the present application; and column 2, line 40 to column 3, line 2 of Khwaja et al.). To resolve this long felt need for a quality control method, a great deal of effort has been directed to the separation and isolation of the biologically active components from botanical materials. But this purification approach diminishes the benefits of complex and synergistic biological activity provided by naturally occurring botanical material (Khwaja et al., column 3, lines 3 to 43). Khwaja et al. attempt to provide a method for producing pharmaceutical grade of St. John's Wort by using compositional and activity fingerprints. However, as discussed above, Khwaja et al. applies fractionation technique to process the samples, i.e., separating and isolating the samples into multiple fractions. Thus, the Khwaja method does not overcome the disadvantage of the purification approach. As shown by paragraph 5 (pages 2 to 4) of the Declaration under 37

C.F.R. §1.132 by Dr. Dan Theodorescu dated March 7, 2005, others have also failed in their attempts to resolve the problem. For example, despite the promising initial clinical data, the clinical trial of BotanicLab's herbal medicine, namely, PC-SPES, was halted due to quality control problems.

In *Graham v. John Deer Co. of Kansas City*, 383 U.S. 1, 17-18, the United States Supreme Court set out an objective analysis for applying §103 rejection where secondary considerations, such as long felt but unresolved needs and failure of others, are considered as important factors against finding of obviousness. In view of the above-discussed long felt but unresolved needs and failure of others in developing a quality control method for assessing herbal compositions, Applicants respectfully requests reconsideration and withdrawal of the present §103 rejection.

In view of the foregoing, Applicants respectfully submit that the claimed method is not rendered obvious by the cited references.

Conclusion

In view of the foregoing remarks, Applicants respectfully request withdrawal of the outstanding rejection and early notice of allowance to that effect. Should the Examiner believe that a telephonic interview would expedite prosecution and allowance of this application, he is encouraged to contact the undersigned at his convenience.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No.50-1283. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Dated: April 30, 2009

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